REMARKS

Status of the Claims

Claims 1-3 were previously presented for examination and were rejected. Claims 1 and 3 have been amended to correct minor typographical errors and clarify the meaning of the claims. Claim 2 has been canceled. New claims 4-12 have been added. Support for the amendments may be found throughout the specification as filed, for example, at page 5, paragraph 2, pages 6-8, in FIGS. 1-5 and in Examples 1-5. Thus, no new matter has been introduced by way of these amendments. Upon entry of the amendments, claims 1 and 3-12 will be pending. Entry of the amendments and examination on the merits are respectfully requested.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Priority Claim

The specification has been amended to include a priority claim to U.S. Provisional Application No. 60/389,474, filed June 18, 2002 in the first sentence.

Objections to the Specification

The specification has been amended to address the objections raised by the Examiner. Thus, these objections may now be withdrawn.

Claim Objections

Claims 1 and 3 have been amended to correct the typographical errors pointed out by the Examiner. Claim 2 has been canceled. Accordingly, these objections should also be withdrawn.

Rejections under 35 U.S.C. § 112

Claim 2 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it depends from itself. Since claim 2 has been canceled, thereby rendering any comments directed to this claim moot..

Rejection under 35 U.S.C. § 102

Claim 1 stands rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Nakao *et al.* (*Genome Informatics* 1999, 10:94-103, hereinafter "Nakao").

The Examiner alleges that Nakao discloses a method of metabolism reconstruction, wherein data regarding the organism's metabolism is collected, the data are linked to metabolic pathways, and interconnections are identified to create a map of the organism's metabolism (the OA at page 5). Applicants respectfully traverse this rejection.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2 d 1655, 1657 (Fed. Cir. 1990)). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131.

As a preliminary matter, claim 1 as amended recites "A method for reconstructing metabolism of a eukaryotic organism in a non-disease state and a disease state, comprising:

(a) collecting data regarding the organism's metabolism for said non-disease and disease states;

(b) linking the data into metabolic pathways;

(c) linking said metabolic pathways to functional information, disease manifestations and/or high-throughput screening information;

(d) identifying interconnections between the metabolic pathways; and

(e) creating maps of the organism's metabolism in said non-disease and disease states by integrating information obtained in steps (a), (b), (c) and (d)."

In order to understand the presently claimed invention, it is important to appreciate its three fundamental components: (1) metabolic reactions and their interconnections forming metabolic pathways/networks; (2) molecular data (genes and proteins); and (3) links between the genes and proteins participating in the metabolic pathways and related diseases or disorders as annotated from the literature. As explained in the present specification at page 8, paragraph 2, "One feature of the reconstruction is the incorporation of human diseases. By activating a link to diseases, a user can see lists of diseases associated with the pathway. From these lists, pages for individual diseases can also be accessed. These pages contain lists of enzymes, reactions, and pathways that have been linked to a disease. In addition, one can view notes describing various aspects of a disease mechanism, its metabolic causes, and/or its manifestations." The ultimate result is a "disease network," comprising metabolic pathways, reactions, compounds and enzymes related to a particular disease (specification at page 6, paragraph 2). Using such a "disease network", it is possible to identify diseases related by common metabolic pathways, reactions, compounds or enzymes, which is a valuable tool for predicting and overcoming adverse drug-drug interactions.

In contrast, Nakao only teaches a method of using gene expression data in order to reconstruct metabolic pathways. Nakao does not teach or even suggest linking disease-specific information to the KEGG database. Neither does it teach or suggest incorporating functional and/or high-throughput screening information. Indeed, much like a number of earlier reports, Nakao's article teaches primarily reconstruction of microbial metabolic pathways. As explained above, integration of disease-specific information within the framework of a metabolic reconstruction makes the system much more relevant to human drug discovery.

Thus, it is apparent that Nakao does not teach every limitation of claim 1 as amended. Since Nakao fails to expressly teach each and every element of the claimed invention, the strict identity standard for anticipation under 35 U.S.C. § 102(b) is not satisfied. Accordingly, Applicants respectfully submit that this rejection may be withdrawn.

Rejection under 35 U.S.C. § 103

Obviousness over Nakao in View of Okubo

Claims 1 and 2 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nakao in view of Okubo *et al.* (*Nature Genetics* 1992, 2:173-179, hereinafter "Okubo").

The Examiner acknowledges that Nakao does not teach using EST data. To cure this deficiency of Nakao, the Examiner cites Okubo, which allegedly teaches the use of EST data for gene mapping. The Examiner argues that it would have been obvious to one of skill in the art to modify the method of metabolism reconstruction of Nakao by incorporating EST data of Okubo because Okubo teaches that a map of expressed genes will facilitate the search for biologically and industrially interesting genes. Applicants respectfully traverse this rejection.

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). To establish a *prima facie* case of obviousness a three-prong test must be met. First, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference to achieve the claimed invention. *KSR* at 1731. And third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Rejections on obviousness grounds cannot be sustained by mere conclusory statements. *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2007) (citations omitted). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Evidence of an unobvious or unexpected advantageous property can rebut prima facie obviousness. MPEP § 716.02(a). Moreover, if a proposed

modification changes the principle of operation of a reference, the teachings of that reference are not sufficient to render the claimed invention obvious. MPEP § 2143.01.VI, citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (emphasis added).

The teachings of Nakao and the current amendments to claim 1 have been discussed above. Okubo merely teaches the use of ESTs in gene mapping. Much like Nakao, Okubo does not teach or suggest linking metabolic pathways to functional information, disease manifestations and/or high-throughput screening information, as recited in claim 1 as amended. As Applicants have explained above, the incorporation of disease-specific information into a database of metabolic networks with gene expression data has the transformative and synergistic effect of generating "disease networks" linking metabolic, genetic and pharmacological data. Consequently, none of the methods disclosed in Nakao and/or Okubo is capable of producing the kinds of information that can be generated using the presently claimed methods.

Thus, Applicants respectfully submit that neither of the cited references, alone or in combination, teaches or suggests linking metabolic pathways to functional information, disease manifestations and/or high-throughput screening information. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing the disease data into the equation, the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the obviousness argument. Therefore, the Office has failed to make a *prima facie* case of obviousness and this rejection under 35 U.S.C. § 103(a) should be withdrawn.

Obviousness over Nakao in View of Karp

Claim 3 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nakao in view of Karp *et al.* (*Trends in Biotech.* 1999, 17:275-281, hereinafter "Karp").

The Examiner alleges that Nakao teaches that the metabolic reconstruction also comprises data regarding metabolism of an organism for both a reference (non-diseased) and perturbed (diseased) state. Nonetheless, the Examiner acknowledges that Nakao does not teach identification

of drug targets. To cure this deficiency of Nakao, the Examiner cites Karp, which allegedly teaches that drug targets can be identified through the analysis of pathway genome databases. The Examiner argues that it would have been obvious to one of skill in the art to modify the method of reconstructing an organisms metabolism of Nakao with the drug target identification of Karp because Karp allegedly shows that that integrated genome-metabolic pathways provide a framework for improved drug discovery. Applicants respectfully traverse this rejection.

As a preliminary matter, claim 3 has been amended to recite: "A method for identifying a drug target comprising:

(a) collecting data regarding a eukaryotic organism's metabolism for a non-disease state and a disease state;

(b) linking the data into metabolic pathways;

(c) linking said metabolic pathways to functional information, disease manifestations and/or high-throughput screening information;

(d) identifying interconnections between the metabolic pathways;

(e) creating maps of the organism's metabolism in said non-disease and disease states by integrating information obtained in steps (a), (b), (c) and (d); and

(f) identifying a drug target by comparing differences between said non-disease and disease states using the maps."

Thus, much like the method of claim 1, claim 3 as amended incorporates linking of the metabolic pathways to functional information, disease manifestations and/or high-throughput screening information. The rationale and important advantages provided by this step have been discussed in detail above. Additionally, claim 3 as amended specifies that the organism whose metabolic pathways are being analyzed is a eukaryotic organism.

The teachings of Nakao have been discussed above. Karp teaches that integrated pathway-genome databases, in conjunction with visualization and analysis software, provide a framework for improved understanding of microbial physiology and for antimicrobial drug discovery. In contrast, the main focus of the presently claimed approach is on eukaryotic metabolic pathways – proteins that may be affected by drugs in order to alleviate a disease. As explained earlier, the main idea of the present invention is that combining the data about what genes/proteins have been linked to a

particular disease in multiple independent studies with information on their roles and positions in eukaryotic metabolic pathways allows reconstructing different versions of pathways (one for health and one for each disease of interest). That, in turn, helps to make a more informed decision regarding drug target identification and selection even in the absence of relevant disease-specific genomics or proteomics data. The disease specific genomics or proteomics data may be used as an additional piece of information to further refine target selection.

Thus, Applicants respectfully submit that neither of the cited references, alone or in combination, teaches or suggests linking metabolic pathways to functional information, disease manifestations and/or high-throughput screening information to facilitate identification of a drug target in a eukaryotic organism. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing the disease data into the equation, the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the obviousness argument. Therefore, the Office has failed to make a *prima facie* case of obviousness and this rejection under 35 U.S.C. § 103(a) should be withdrawn.

Double Patenting Rejection

Claim 3 stands provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claim 1 of copending Application No. 11/499,437. The Examiner alleges that although the preambles of claim 3 of the present application and claim 1 of Application No. 11/499, 437 are different, the scope of the claims is the same because both claim 3 of the present application and claim 1 of Application No. 11/499, 437 are directed to the same use, perform the same steps, produce the same result and recite identical claim language in the body of the claims.

As discussed above, claim 3 of the present application has been amended to include additional limitations not found in claim 1 of Application No. 11/499, 437, which is a continuation-in-part of the present application. Accordingly, Applicants respectfully submit that this double patenting rejection should be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **655202000300**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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